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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/966,147	09/27/2001	Leonard G. Presta	GENENT.33CPC4C	4067

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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 03/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/966,147	PRESTA ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *21 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,4-7 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 4-7, 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/21/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CAR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 21, 2004 is acknowledged and has been entered. Claim 1 has been amended. An action on the RCE follows.

2 Claims 1, 4-7 and 23 are pending and currently under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

4. Applicant points to Serial No. 08/215,139 filed on March 18, 1994 for support for the claimed invention in which the use of trkC antibodies for the treatment of axonal sprouting in epilepsy is mentioned at page 88. The argument has been considered but has not been found persuasive because the anti-trkC antibodies mentioned are not drawn to binding between residues 32 and 839 of SEQ ID NO:6. The priority date for the claimed invention remains at August 5, 1994.

Claim Rejections - 35 USC § 112

5. Claims 1, 4-7 and 23 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in the papers mailed July 23, 2004, section 4, pages 2-5 and mailed January 15, 2004, Section 9, pages 5-11.

Applicant argues that the art recognized that there was a relationship between trkC, NT-3, neuronal sprouting and epilepsy at the time the application was filed and this recognition, in combination with the statement on page 68 that

"this antagonist activity is believed to be useful in the treatment of pathological conditions associated with endogenous neurotrophin production such as aberrant sprouting in epilepsy" would be understood by one of ordinary skill in the art to provide an explicit connection between trkC of SEQ ID NO:6, aberrant neuronal sprouting and a disease. The argument has been considered but has not been found persuasive for the reasons set forth previously.

Applicant points to Babb et al, 1991 IDS item, in which new synapse formation was found in hippocampal tissue removed from human epileptic patients but not in hippocampal tissue removed from normal human patients. Represa et al, 1990 IDS item, , a review by Ben-Ari and Represa, 1990 IDS item, Babb, 1997 IDS item, Scharfman, 2002 IDS item who report evidence similar to that of Babb et al, 1991 and corroborate that neuronal sprouting in epilepsy was known in the art since the 1990's.

Applicant points to Bengzon et al, 1993 IDS item, McNamara, 1994 IDS item, to demonstrate that the art recognized that trkC and NT-3 were each altered in animal models of seizure activity, that it was known in the art at the time the application was filed that trkC levels were changed during seizures and that methods affecting trkC or NT-3 levels or activity would be expected to be useful to affect neuronal sprouting and to be useful for treating epilepsy. Applicant states that this has been corroborated by findings that local increases in NT-3 can induce sprouting as set forth in Zhou et al, 2003, IDS item.

Applicant argues that the recitation, in claim 1, of an antagonistic antibody which specifically binds to a sequence within amino acid residues 32 and 839 of SEQ ID NO:6 limits the claimed invention to methods using antibodies directed to this specific portion of the explicitly identified amino acid sequence. This, in

combination with the submitted references establishes a nexus between a trkC of SEQ ID NO:6 and aberrant sprouting in epilepsy which would have been recognized as such by one of ordinary skill in the art.

The argument and the submitted references have been considered but have not been found persuasive. The references drawn to neuronal sprouting have been considered but are not found persuasive because, although the association between neuronal sprouting and epilepsy was well known in the art at the time the invention was made, nothing in any of these references suggests an association between that sprouting and "a" TrkC as suggested by Applicant.

As drawn to the Bengzon et al reference, the reference has been considered but is not found persuasive given that the data presented in the reference is not commensurate in scope with the claimed invention and is not drawn to protein, but rather to mRNA levels. The reference provides no nexus between trkC (SEQ ID NO:6) protein antagonism, NT3 and neuron sprouting or any pathological condition. In particular, the reference is drawn to the detection of mRNA levels for trkC and NT3 in rats that have been synthetically stimulated to have seizures. The reference concludes that seizure activity sets in motion a constellation of changes in gene expression for neurotrophins and their receptors and that in dentate granule this includes increased trkC mRNA levels and decreased NT3 levels (p. 444, col 1). Upon increase of transcription of trkC mRNA, NT3 transcription is reduced (p. 444, col 2). The functional consequences of the observed changes of neurotrophins and their receptors during kindling development and in response to seizure activity are still unclear. Finally, an important role for plastic changes and synaptic reorganization occurring during kindling epileptogenesis seems possible (p. 444, col 2). As set forth above, the

reference provides no nexus between trkC (SEQ ID NO:6) protein antagonism, NT3 and neuron sprouting or any pathological condition.

As drawn to the McNamara reference, a review of the reference reveals that those of ordinary skill clearly differentiate between "epileptic" and "non-epileptic" seizures, that is seizures that are evoked in normal brain and epileptic seizures when occurring without apparent provocation. The reference teaches that there are more than 40 individual epileptic syndromes described in human and at least eight familial forms have been described in which genetic determinants appear to be prominently involved and that the study of epilepsy is in its infancy (p. 3420, col 1). The reference emphasizes the "great heterogeneity" of disorders labeled as epilepsy and teaches that this heterogeneity is daunting (p. 3422, col 2). Different families that show genetic epilepsy have been shown to exhibit different chromosomal localizations for epilepsy linked genes (pages 3420-3421). In the future, it seems likely that molecular genetic approaches will elucidate the molecular etiologies of epilepsies in mice which should expedite discovery of molecular etiologies of additional familial epilepsies in human. Gene targeting approaches will permit testing whether a putative cellular and molecular mechanism identified in reduced preparation is causally linked to the epileptic phenotype in the intact mammalian nervous system. Together, these emerging insights should lead to novel and rational therapies based upon knowledge of disease mechanisms (p.3422, last paragraph). Although Applicant points to page 3419 for support of the nexus between trkC and NT3 and neuronal sprouting, the reference does not mention NT3. Instead, the question "What is the molecular basis of sprouting?" is posed. The reference then goes on to disclose two references, one, not submitted herein and the other the Benzon et al reference

discussed above. The reference concludes that TrkC, NGF and BDNT may form part of the molecular machinery responsible for pathological morphologic rearrangements (p. 3419, col 2). Given the teachings set forth above, it is clear that those of skill in the art, represented by these two references, did not recognize a predictable nexus between trkC, NT3 and aberrant neuronal spouting or any pathological condition. Further, epilepsy was know to be a greatly heterogeneous disease with apparent differences in genetic sites of mutant genes and even if it were to be found that trkC and/or NT3 is in fact a rational target for inhibition of aberrant neuron sprouting or the treatment of any pathological condition associated with elevated NT3 in some patients, the specification provides no guidance on how to chose the patients that would be treatable with the claimed invention.

As drawn to the Zhou et al reference, this reference does not provide a nexus as suggested by Applicant because it is drawn only to a demonstration that virally induced overexpression of NT3 resulted in local, sustained expression of NT3 and supports plasticity of intact CST axons after trauma-induced denervation. The reference does not discuss trkC, does not discuss aberrant sprouting, does not discuss epilepsy.

These references in combination with the wording of the claim 1 do not establish a nexus between a trkC of SEQ ID NO:6 and aberrant sprouting in epilepsy and no one of ordinary skill in the art would believe it more likely than not that the invention would function as claimed based only on the single statement in the specification and the art of record.

Applicant admits that the antibody that specifically binds to a sequence within amino acid residues 32 and 839 of SEQ ID NO:6 will bind not only to SEQ ID NO:6 but also to splice variants of human trkC. Applicant argues that "the

recognized relationship between trkC, aberrant sprouting and a disease in need of treatment being clear, the Examiner's concern that a "particular trkC" need be identified is believed to be unwarranted. Applicant further presents reasons why "any" trkC would be useful in the claimed invention. The arguments have been considered but have not been found persuasive because no nexus has been established between any trkC, aberrant sprouting or any disease in need of treatment for the reasons set forth previously and above.

Applicant argues that since the claims are directed to the use of antibodies that bind to the full-length trkC receptor of SEQ ID NO:6 without the associated signal sequence, any issues concerning the potentially different biological activities of the various splice isoforms no longer apply. The argument has been considered but has not been found persuasive because the specification clearly teaches the differential effects of trk splice variants on signal transduction and it is not clear how Applicant's arguments drawn to signal sequences overcomes the rejection.

Applicant argues that even if non-productive receptors act to sequester the antagonistic antibodies of the invention, one can of course predict that the effect of such sequestration would likely affect the dosage of the antagonistic antibodies needed and such effects are well known and may be accounted for by routine experimentation. The argument has been considered but has not been found persuasive. For the reasons of record, it cannot be predicted that the invention will function as claimed because no nexus has been provided between trkC receptor of SEQ ID NO:6 and aberrant neuron sprouting or any pathological condition. Even if such a nexus were to be found the specification provides no information on non-productive receptors and no information on how to use the invention so that it will function as claimed.

The arguments have been considered but have not been found persuasive and the rejection is maintained for the reasons of record.

6. Claims 1, 4-7 and 23 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in the papers mailed July 23, 2004, section 5, pages 5-6 and mailed January 15, 2004, Section 10, pages 11-15.

Applicant reiterates arguments drawn to the nexus between trkC sequence and aberrant neuron sprouting and epilepsy at the beginning and at the end of the section drawn to written description. The arguments have been considered previously and above and have not been found persuasive.

Applicant argues that the claimed antagonists are antibody antagonists and are directed against SEQ ID NO:6. The preparation of antibodies is described in the specification and the making of antibodies is within the skill of the art. The argument has been considered but has not been found persuasive. Although the specification teaches the making of antibodies, the claims as currently constituted are drawn to methods of treatment wherein the antagonistic antibodies bind to splice variants of SEQ ID NO:6. Since the claims are drawn not only to full length SEQ ID NO:6, but also to splice variants thereof and the specification provides no information on which amino acids, within amino acids 32-839 of SEQ ID NO:6, that the antibodies must bind in order to function as claimed, the teachings of the specification do not provide an written description of the claimed invention that will satisfy the written description requirements of 35 USC 112, first paragraph.

Applicant argues that there is no absence of knowledge as to what the material consists of. The argument has been considered but has not been found persuasive since neither the specification nor the art of record provide information as to which, if any, known or unknown splice variant of SEQ ID NO:6 is

associated with aberrant sprouting or any pathological condition. It is clear that there is indeed an absence of knowledge as to what the material consists of.

Applicant reiterates arguments drawn to antibodies directed to a sequence within amino acid residues 32-839 of SEQ ID NO:6. The arguments have been considered but have not been found persuasive for the reasons set forth above. Although a specific amino acid sequence is recited, there is no teaching as to which piece of this sequence is associated with the claimed invention.

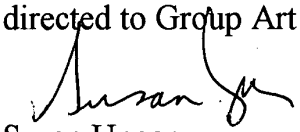
The arguments have been considered but have not been found persuasive and the rejection is maintained.

7. All rejections have been maintained and no claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.



Susan Ungar
Primary Patent Examiner
March 21, 2005